Comprehensive Care for Hemophilia and Related Inherited Bleeding Disorders: Why It Matters

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Comprehensive hemophilia treatment centers (HTCs) were first inaugurated more than 50 years ago. In 1976, a federally funded HTC network was created in the United States, making multidisciplinary care for patients with hemophilia and other inherited bleeding disorders available throughout the country for the first time. Education of the patient and healthcare professional in the management of bleeding became a mainstay of these programs. The HTCs began surveillance of the complications of treatment, such as hepatitis and HIV. The high rate of HIV infection in the hemophilia population from contaminated clotting factor concentrates forced an adaptation of HTCs to manage the medical and psychosocial consequences of these diseases. In addition, expanded surveillance for potential new therapy-associated complications became a legacy of these efforts. From the HIV era until the present, HTCs have undertaken expanded clinical research (drawing on a new scientific understanding regarding hemostasis and new knowledge regarding the management of quality of life) to study new methods to improve the well-being of patients with hemophilia. The further research has extended to phase 1 gene transfer trials for hemophilia A and B. Although the prospect for a complete cure for patients with hemophilia is some time away, HTCs in the 21st century continue to vigorously research a cure. In the interim, the HTC model continues to provide essential services that are being reassessed in light of new scientific information to prevent the complications that have defined the clinical picture of hemophilia.

Introduction

Understanding of the pathogenesis of hemophilia A and B and other inherited coagulopathies has increased exponentially since the 1950s. Evolving in parallel with this scientific knowledge has been a model of clinical care delivery that relies on a team of multiply trained healthcare professionals under the direction of a hematologist to provide acute and chronic care to patients with these diseases. For several decades, the strategy has been formalized as a process and a clinical setting under the designation of comprehensive hemophilia (diagnostic) and treatment centers (HTCs). This model has been applied in many countries and has become, with the endorsement of the patient communities, a mainstay of care for these diseases. In this paper, I examine the impact on the bleeding community, the professionals caring for these patients, and on societal health services. Despite that this assessment is made by a hematologist with clear allegiance to this clinical model, every attempt will be made to provide supportive scientific data to examine the actual impact of the model on patient outcomes. However, before these impacts are presented, an examination of how and why HTCs came to be is essential to explain how a concept pioneered more than 50 years ago is still germane to the care of hemophilia and other bleeding disorders in the 21st century.

History of Comprehensive Care

The concept of developing specialized centers for the care of people with hemophilia originated in the United Kingdom at the end of the 1940s [1,2,3••]. It was recognized that patients with hemophilia are examined rarely by general practitioners. However, the treatment and patient education the practitioner may need is specialized. Biggs [3••] stated that it was for this reason that the Ministry of Health and the Medical Research Council of the United Kingdom created special HTCs. First established in 1954, the emphasis of HTCs was on diagnosis and the need to avoid dangerous operations [2]. These 18 HTCs did little more than diagnose the patients, issue special identity cards to them, and provide them psychosocial support to protect them from the many hazards of hospital treatment.

The HTCs provided outpatient facilities for patients with hemophilia A and B who did not require an admission to the hospital, educated other hospital staff and patients on the relevant aspects of hemostasis, educated

patients on how to give themselves intravenous infusions, acted as a liaison for social and welfare services, and collaborated with other HTCs for research [4].

Expertise provided by the subspecialist in these HTCs supplemented, rather than replaced, basic medical care provided by the general practitioner [3••]. The education of these practitioners proved beneficial for extending the influence of HTCs into remote locales. This influence gave rise to a regionalization of specialized hemophilia care. Before the initiation of these centers in the mid 1950s in the United Kingdom, an adult hemophiliac was scarcely seen by practitioners because many patients died before the age of 15 years. In the 1960s, clotting factor concentrates (CFCs) replaced whole blood and early plasma fractions. Thereafter, the lifespan and the quality of life administered for patients with hemophilia increased in the United Kingdom [3••].

Another basic tenet of HTCs was their multidisciplinary approach. Successful specialized orthopedic surgery required a close working relationship between the hematologist and orthopedic surgeon. Summarizing an experience from 117 orthopedic procedures in patients with hemophilia, de Palma and Colter [5] stated, "Surgery in the hemophiliac is dangerous and should never be attempted except in those cases in which all other means have been exhausted and then only if the patient's blood is shown to be at least somewhat coagulable and the physical equipment is available to administer adequate pre- and postoperative management."

In addition, psychosocial professionals provided key assessment and therapeutic skills for patients followed in these HTCs. Interview data gleaned from 40 severely affected boys and men with hemophilia (36 with hemophilia A and four with hemophilia B) attending two of the hemophilia centers in the London area (St. Thomas and Lewisham Hospital) clearly indicate a positive impact from this multidisciplinary modality. Nearly threefold greater adverse experiences were observed outside centers compared to within HTCs [6]. Data from one woman with combined factor V and factor VIII deficiency indicated that from the very early days, HTCs treated other bleeding disorders besides hemophilia A and B.

Coincident with the recognition of the role that specialized centers may play in the care of hemophilia and acknowledging the experience in the United Kingdom, several HTCs in the United States were developed or expanded. Natural history data on 44 patients with hemophilia from 1937 to 1963 summarizes pre-HTC and early HTC experiences [7]. Poor outcomes in the early years could be attributed not only to a lack of adequate hemostatic replacement but to insufficient collaboration among physician specialists, inadequate facilities, and a need for better diagnostic capabilities. A positive impact on outcome as each component was added encouraged implementation of the HTC model. Examples include decreased transfusion reactions over time, shorter hospitalizations for acute bleeding and postoperatively, and decreased spontaneous intracranial hemorrhage in children.

Approximately 17 years elapsed from the initiation of hemophilia centers in the United Kingdom until there was formal recognition by government agencies in the United States of the importance of HTCs, although several states initiated HTCs earlier [8,9,10•]. Data documenting the need for a nationwide comprehensive healthcare system for hemophiliacs in the United States and lobbying by patients through the National Hemophilia Foundation (NHF) were required for a national HTC system to be funded. Data on 100 hemophiliacs from one HTC in 1975 demonstrated the need and the positive impact of HTC care. There was an expected high incidence of hemophilic arthropathy and other clinical and laboratory abnormalities, but the interventions had reduced selected morbidities significantly (*eg*, severe dental disease). The authors concluded that data gathered in specialized settings of comprehensive care would greatly enhance the understanding of the natural history of hemophilia and the impact of therapeutic maneuvers [10•].

A pioneering HTC on the West Coast assembled a large multidisciplinary team (hematologist, pediatrician, internist, orthopedist, physical therapist, dentist, oral surgeon, public health nurse, intravenous nurse, medical photographer, psychiatric social worker, clinical psychologist, psychiatrist, rehabilitation counselor, and occupational therapist). Rehabilitation services for patients with hemophilia, research and medical in psychosocial aspects of hemophilia, and education of the professional community and expanded diagnostic laboratory capabilities were developed [11]. Published data from this HTC established the exigency for a nationwide network of HTCs.

The United Kingdom and the United States were certainly not unique in acknowledging the need for specialized centers for patients with hemophilia. Several French hematologists established a boarding school for boys with hemophilia, and two other schools were subsequently opened in 1963 and 1965 [12]. Between 1960 and 1972, approximately 50% of the boys (ages 6–25 years) with hemophilia in France spent 1 year or more in such an institution. Out of this experience, a model of optimal care for hemophilia evolved in France that permitted each of these patients to benefit from the expertise of a full multidisciplinary team. At its peak, more than 100 boys with hemophilia were present in the largest center for an average of 260 days per year. In addition, it provided the investigators the opportunity to measure the psychosocial and psychologic impact of the disease (important contributions to the world medical literature on hemophilia).

In Australia, the concept of comprehensive care evolved in a more traditional fashion, silmilar to the pathway of the United States and United Kingdom models. Beginning in 1957, a specialized hemophilia clinic at the Royal Prince Alfred Hospital was developed with the research and a clinical care component, with special expertise in blood banking and production of CFCs locally. Japan, Italy, and Israel developed independent HTC sites that evolved into nationwide networks [13–15].

In the United States, the culmination of these early insights into the benefits of comprehensive care was the

creation of the National HTC Program. Created by Congressional legislation in 1975, Section 1131 of the Public Health Service Act provided for the establishment of Hemophilia Diagnostic and Treatment Centers to serve geographic areas throughout the United States. Three million dollars per year was appropriated initially to fund 22 HTC affiliates. Each HTC met 13 distinct requirements for funding: a coagulation laboratory of defined standards; a blood bank of defined capability with appropriate blood product resources; a plan for developing or evidence of an existing multidisciplinary team; (consisting of) a hematologist, internist, pediatrician, orthopedic surgeon, oral surgeon or dentist, physical therapist, registered nurse, and a social worker; the availability of a psychologist or psychiatrist, genetic counselor, educational/vocational rehabilitation counselor, and a nutritionist; capability to instruct patients/family members in administration of replacement therapy in a home setting; provision of a written comprehensive care plan developed in consultation with the patient's primary physician provided to each patient; establishment of an outreach program to encourage all hemophiliacs and healthcare providers in the geographic area served by the project to participate in the program; training (to the extent of the resources permitted) of professional and other personnel in knowledge and care of hemophilia; commitment to collect reimbursement from third-party payors; establishment of a database for reporting outcomes; community participation through the creation of an advisory council; and creation of a patient information source. It is the legacy of this legislation, and similar governmental commitments internationally, that has become our existing HTC network. The discussion of its impact will provide the basis for why comprehensive hemophilia care matters [16].

The Impact of Comprehensive Care in the First Decade After Implementation

One of the first reports on the impact of the HTC legislation (1982) was a socioeconomic evaluation of a state funded comprehensive hemophilia care program that was an affiliate of the national program [17•]. This cost-efficacy study ascertained that by the fifth year of funding, 77% of patients with hemophilia in the state received total care through this HTC (28 of 43 patients converted to home infusion, most of whom had previously not had such self-infusion capacity available). The number of hospital days per patient decreased from 12.6 to 3.5, the number of visits to hospital facilities decreased from 34 to 2.4, and the yearly cost of clotting factor stabilized at $7000, resulting in a net savings of approximately $10,000 per patient primarily from reduced hospitalization cost. In addition, the number of days lost from school and work decreased twofold and threefold, respectively. In an accompanying editorial, Aledort [18•] described the impact that this could have on a nationwide system where there was an increasing competition among chronic diseases for precious healthcare dollars. He also emphasized the positive impact of converting from an inpatient to an ambulatory setting, with increased quality of life and fiscal savings to the families and to the overall system.

A 5-year multicenter study examined the benefits of comprehensive care from 11 of 22 federally funded comprehensive centers. The cohort of 4682 patients receiving comprehensive care was compared to 1333 patients who received care from the same providers before the creation of the comprehensive care model. There were several notable differences. The average days lost from work or school were reduced to 33%, the average days spent for inpatient care were reduced from 9.4 to 1.8, the patients who were used with job-provided insurance had increased from 74% to 93%, out of pocket expenses had decreased from $850 to $342, and the overall cost of patient care per year declined to 30%, from $15,800 to $5932. In addition, the number of unemployed adults decreased from 36% to 12.8%. These data demonstrate that comprehensive care has a dramatic impact on the physical outcome, social habilitation, and overall cost to society. Other single center reports support this conclusion [19•].

A stated aim for comprehensive HTCs is the development of educational tools for the professionals providing care for children and adults with hemophilia. As a direct outgrowth of the HTC network, these publications became much more available in the United States and worldwide. Notable instruction tools were created for nurses, psychiatric and psychosocial professionals, dentists and oral surgeons, surgeons performing reconstructive and orthopedic procedures, and rehabilitation specialists and physiotherapists [20–25]. In addition, full textbooks regarding comprehensive management of hemophilia were published in the United States for the first time [26]. Experts in all facets of hemophilia created a manifest for professionals caring for these patients.

Comprehensive Care During the AIDS Era

In July 1982, the Centers for Disease Control and Prevention (CDC) described three adults with hemophilia who had *Pneumocystis carinii* secondary to immune deficiency, a clinical syndrome shown primarily in the homosexual population [27]. In the subsequent months, it became apparent that a significant percentage of patients with hemophilia were infected with an immune deficiency virus (HIV). In one study by Eyster *et al.* [28], upwards of 90% of patients with severe hemophilia A were infected. This new morbidity challenged HTCs in ways that previously had been unthinkable. The mortality rate among hemophiliacs rose exponentially and severely debilitated patients became common. Although nearly all the patients contracted HIV from infected CFCs, there were accompanying risks of further heterosexual or homosexual transmission (transmission from the homosexual population to others could not be ignored). A moral onus existed for HTCs to participate in preventive strategies against the spread of this lethal disease [29]. Psychosocial methodol-

ogies were adapted as risk reduction strategies to educate sexually active HIV-infected patients with hemophilia to reduce their likelihood of spreading the disease to a sexual partner. A body of medical literature evolved that established hemophilia and HTCs as leaders in the early phase of developmental programs of risk reduction among heterosexual populations. By 1987, 48 of 72 hemophilia centers were using formal pre- and posteducation knowledge testing with their patients and their patients' sexual partners. In addition, innovative risk reduction programs were designed and implemented by HTC psychologists for adolescents with hemophilia to teach the prevention of the spread of HIV and to explore human sexuality and intimacy in a nonthreatening method [30,31•]. A similar expansion of responsibilities for the care of HIV in patients with hemophilia occurred in European treatment centers [32]. Many seminal research publications on the pathogenesis of HIV benefited from the participation of patients with hemophilia and the establishment of cohorts that helped to define the natural history of HIV in young children, adolescents, and adults [33–37]. In addition, these cohorts contributed to large research studies that characterized some of the key immunologic predispositions for HIV, such as chemokine receptors [38].

The scourge of HIV did not accelerate after the advent of CFC purification techniques (*eg*, heat treatment and solvent detergent). However, the impact of this decade-long commitment by HTCs to the care of people with HIV, and to their family members who may be at risk because they were sexual partners of the patient with hemophilia, had a profound influence on their evaluation. It demonstrated tangible evidence of the capacity of this multidisciplinary model to adapt to the most catastrophic of medical challenges.

The Key Role of the Diagnostic Laboratory for Hemophilia Treatment Centers

The capacity to accurately diagnose coagulopathies constitutes a major keystone for all comprehensive care programs. In the 50 years since the first initiation of comprehensive care in the United Kingdom, these capacities have grown significantly. The techniques developed in the 1950s to diagnose and differentiate hemophilia A and B (factor VII and IX assays, respectively) were the first of many laboratory advancements that enabled HTCs to fulfill their mission. Other genetically controlled coagulation proteins (*eg*, procoagulants and anticoagulants), the deficiency of which causes human disease, have been isolated, protein sequenced, DNA sequenced, and knocked out in animal models in the past 50 years [39,40]. The typical HTC laboratory evolved from the ability to screen for coagulopathies and diagnose specific factor assay deficiencies (*eg*, factors VIII, IX, and XI) to the assessment of platelet function and differentiation of subtypes of von Willebrand disease. Capacities to genotype subsets of patients with coagulopathy and apply the knowledge to predicting clinical morbidities and expected response to therapies have been implemented in HTCs.

This capacity has benefited from the ongoing commitment of hematologists and other experts in the HTCs to publish new findings in the fields of diagnostic hemostasis and thrombosis and the integrated nature of clinical hemophilia with clinical and basic research in hemostasis. The World Federation of Hemophilia, in its role in creating International Hemophilia Training Centers, has played a major role in expanding diagnostic technologies from the developed world to many countries in the developing world [31•]. The strategy has been to train the physicians and other scientists from the developing countries. Then, by providing these human and other resources, when these physicians return to their home countries, hemostasis diagnostic laboratories can be implemented in an expeditious fashion.

In addition, the NHF and the Canadian Hemophilia Association have played important roles in providing funding for the training of new scientists and physicians in the field of hemostasis and thrombosis. With the Judith Graham Pool Fellowships at the NHF, a generation of hemophilia treaters in the United States has received support for advanced training in the field of hemophilia [41]. These conjoined efforts by the government, consumer professional organizations such as the NHF, and HTCs have resulted in the establishment and expansion of the infrastructure for the care of people with hemophilia and other hemostatic disorders.

An Enhanced Surveillance Role for Hemophilia Treatment Centers

With the funding from the CDC in 1986 for AIDS care and risk reduction, the CDC has played an important role in funding for HTCs. This has augmented the original sponsorship by the Bureau of Maternal and Child Health of the Health Resources Services Administration in supporting the HTC network. This funding allowed for an expanded regional network of HTCs capable of providing broader care and wider surveillance of hemophilia and the associated morbidities. This surveillance has evolved from an HIV-focused effort to an effort that monitors morbidities and mortalities related to bleeding.

An important pilot effort was the CDC-sponsored six state surveillance project. This surveillance system was a cooperative effort between the CDC and the health departments and federally funded HTCs of Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma. It was designed to identify and collect a wide variety of information regarding all people with hemophilia residing in those six states [42•]. This was the first time this permitted an accurate assessment of the total number of people with hemophilia in the United States.

Application of age-specific prevalence rates from Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma resulted in important definitive epidemiologic data (estimated national population of 13,320 cases of hemophilia A and 3640 cases of hemophilia B [1996–1997], an incidence of hemophilia A births of one in 5032

live male births [1982–1991], and a mean and median age of 25.4 and 23 years, respectively) [43••]. Corresponding death and morbidity data on the 2950 patients (followed for an average of 2.6 years for 7575 person years of observation) were as follows: 236 patients died during the observation period, an age adjusted mortality rate of 40.4 deaths per 1000 person years, and 65% of the deaths were HIV related. Other independent risk factors and their respective relative risk (RR) were AIDS (RR = 33.5; $P < 0.0001$), HIV infections (RR = 4.7; $P < 0.001$), liver disease (RR = 2.4; $P < 0.001$), and low social economic status that is assessed with Medicare or Medicaid insurance reimbursement participation as a surrogate (RR = 1.4; $P \leq 0.01$). The most important finding with regards to the impact of HTCs was undoubtedly the finding that persons who received care in an HTC had a significantly decreased risk of death (RR = 0.6; $P < 0.002$). This finding was true, despite that HIV infection and severe liver disease had higher prevalence among patients receiving care in HTCs compared to patients receiving care elsewhere [43••].

The gathering of this important epidemiologic data in the six states led to the development of a more comprehensive data for all federally funded HTCs in the United States ($n = 144$; Universal Data Collection). This project, initiated in 1999, involves collecting serial blood samples for surveillance for blood borne pathogens, including hepatitis, HIV, and other recognized transfusion transmitted disease viruses and unrecognized pathogens (retroactively assayed in the stored frozen plasma specimens). In addition, epidemiologic and clinical data, including range of motion measurements of the six major joints affected by hemophilia, bilateral elbows, ankles, and knees are made at each HTC assessment [44]. This assessment of the impact of evolving care and surveillance for any potential or actual risks for blood borne infections provides essential longitudinal data to reinforce to the government and society why HTCs matter.

Present and Future Role of Comprehensive Hemophilia Treatment Centers

It is considered a standard in developed countries for patients with hemophilia and other inherited bleeding disorders to have access to multidisciplinary care teams situated in comprehensive HTCs and their affiliated entities. Efforts by the World Federation of Hemophilia, working in consort with the World Health Organization and national health administrations, continually extend the model to developing countries [28]. HTCs and their alliance networks have established guidelines for care that are gradually becoming standards. In the United States, the Medical and Scientific Advisory Council for NHF has a series of Care Recommendations that are continually updated and disseminated widely (Medical and Scientific Advisory Council Rec. 141) [45]. In addition, the Association of Hemophilia Clinic Directors of Canada has published and continuously updated Clinical Practice Guidelines for diagnosis, management, and care of hemophilia and von Willebrand disease [46]. Through the constant scrutiny of these guidelines, hemophilia care will evolve commensurate with new scientific knowledge, clinical data, and ethical, economic, and societal understandings.

An important element is the fiscal burden the treatment of hemophilia and other congenital bleeding disorders confers on the patient and society. Survival and other data support the requirement for perpetual expenditures to maintain and extend the evolving level of care (*eg*, the provision of prophylactic infusion therapy for most children and adolescents with severe hemophilia A and B to prevent the formerly inevitable chronic joint disabilities) [47]. To justify these costly expenditures for better outcomes, including immune tolerance induction to eradicate factor VIII inhibitors, efforts are being initiated to accurately assess the quality of life as a measurable assessment of the impact on patients receiving these intense therapeutic regimens [48–53]. Once hemophilia-specific validated quality of life measures are made, they can be applied to data on cost of care to define a cost efficacy for interventions [54].

A positive economic by-product of care in HTCs for some patients has been the participation in clinical trials of new generation recombinant and plasma-derived CFCs. In the United States, many patients with private health insurance have been constrained by lifetime ceilings or caps on their reimbursement coverage. These patients, when they have chosen to participate in clinical trials with the new CFCs, have often been permitted to be treated with the CFCs exclusively until the product has received regulatory US Food and Drug Administration approval (often many months). Therefore, these patients have extended their lifetime insurance maximums (caps) for a corresponding period of time, increasing the likelihood that they can identify other payor options before their cap is reached. Similarly, for patients on state or federal health payor programs, such as Medicaid or Medicare, participation through HTCs in these trials has saved these programs significant expense, freeing resources for other needy patients [55].

Hemophilia treatment centers proceed into the 21st century as mainstays for hemophilia care, with new possibilities for extending care to cure emerging. Early clinical trials of gene transfer for hemophilia A and B have been designed and conducted by scientists and clinicians closely aligned to HTCs and research participants were recruited by collaborating physician/scientists in the HTC network [56,57]. HTCs provide an ideal capacity for providing longitudinal follow-up of patients in these trials, which is distinct from but complementary to the comprehensive care in these same HTCs. This phenomenon provides another indication that HTCs are adaptable to accommodate future advances in care.

Conclusions

Comprehensive multidisciplinary care for hemophilia began as a concept more than 50 years ago. It has evolved in parallel settings in developed countries around the world. The care

model was flexible enough to extend care to patients with hemophilia who, by virtue of their therapy for their bleeding disorder, developed HIV infection. Where specialized expertise was not available, HTCs developed new skills or recruited professionals with the needed skill sets. Safe pathogen-free CFCs permitted expanded preventive strategies to reduce or eliminate these morbidities of hemophilia and other congenital bleeding disorders and new therapies, such as prophylactic infusions, on a regular schedule have begun the process of eliminating joint disease. These and other similar evolutions in care have contributed continuously to the rising expectations for better clinical outcomes to which HTC professionals ascribe. The comprehensive HTC model represents among the most studied and most successful of care models for the care of inherited disease that causes chronic morbidities. The expansive medical literature that publishes new scientific data providing an enhanced understanding regarding hemostatic disorders engenders expanded clinical sciences dedicated to better diagnosis, treatment, prevention, and cure of hemophilia and other inherited bleeding disorders.

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